Beta-Blockers
Therapeutic Class Review (TCR)

September 1, 2017

Please Note: This clinical document has been retired. It can be used as a historical reference.

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Beta-Blockers: Single Agents		
acebutolol (Sectral®)[1]	generic, Promius	Hypertension (HTN) Ventricular arrhythmias
atenolol (Tenormin®)[2]	generic, Almatica	Angina pectoris HTN Myocardial infarction (MI)
betaxolol[3]	generic	HTN
bisoprolol[4]	generic	HTN
carvedilol (Coreg®)[5]	generic, GlaxoSmithKline	Mild to severe heart failure (HF), to reduce the risk of hospitalization and improve survival HTN Reduce risk of death following MI with left ventricular dysfunction (LVD) in patients with or without HF symptoms
carvedilol (Coreg CR®)[6]	generic, GlaxoSmithKline	
labetalol[7]	generic	HTN
metoprolol succinate ER (Toprol XL®, Kapspargo Sprinkle)[8,9]	generic, AstraZeneca Ohm/Sun	Angina pectoris HF – New York Heart Association (NYHA) Class II or III HTN
metoprolol tartrate (Lopressor®)[10]	generic, Validus	Angina pectoris HTN MI
nadolol (Corgard®)[11]	generic, US Worldmeds	Angina pectoris HTN
nebivolol (Bystolic®)[12]	Allergan	HTN
pindolol[13]	generic	HTN
propranolol[14]	generic	Angina pectoris Cardiac arrhythmias Essential tremor HTN Hypertrophic subaortic stenosis Migraine prophylaxis MI Pheochromocytoma
propranolol (Hemangeol™)[15]	Pierre Fabre	Proliferating infantile hemangioma requiring systemic therapy
propranolol ER (Innopran XL®)[16]	Akrimax/ANI	HTN
propranolol ER (Inderal® XL)[17]	Mist/ANI	HTN
propranolol LA (Inderal® LA)[18]	generic, Akrimax/ANI	Angina pectoris HTN Hypertrophic subaortic stenosis Migraine prophylaxis
sotalol (Betapace®)[19]	generic, Covis	Ventricular arrhythmias
sotalol (Betapace AF®)[20]	generic, Covis	Maintenance of normal sinus rhythm in atrial fibrillation/flutter
sotalol (Sotylize®)[21]	Arbor	Ventricular arrhythmias Maintenance of normal sinus rhythm in atrial fibrillation/flutter

HF = heart failure HTN = hypertension; LVD = left ventricular dysfunction; MI = myocardial infarction

FDA Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Beta-Blockers: Single Agents *(continued)*		
timolol[22]	generic	HTN Migraine prophylaxis MI
Beta-Blockers: Combination Products with Diuretics*		
atenolol / chlorthalidone (Tenoretic®)[23]	generic, Almitica	HTN
bisoprolol / hydrochlorothiazide (Ziac®)[24]	generic, Teva	HTN
metoprolol succinate / hydrochlorothiazide (Dutoprol™)[25]	generic, Concordia	HTN
metoprolol tartrate / hydrochlorothiazide[26]	generic	HTN
nadolol / bendroflumethiazide (Corzide®)[27]	generic, Pfizer	HTN
propranolol / hydrochlorothiazide[28]	generic	HTN

HF = heart failure HTN = hypertension; LVD = left ventricular dysfunction; MI = myocardial infarction

* Combination products are not indicated for initial therapy of HTN.

ˢ Kapspargo Sprinkles were FDA-approved via the 505(b)(2) pathway, in which approval relied, at least in part, on data not developed by the applicant.[29]

OVERVIEW

Beta-blockers are approved for a variety of conditions. This review will focus on the following cardiovascular (CV) uses of beta-blockers: hypertension, heart failure, angina, myocardial infarction, and cardiac arrhythmias.

Hypertension

Approximately 75 million (32%) of adults in the United States (U.S.) have hypertension; the highest prevalence is among African American men and women at 43% and 45.7%, respectively[30,31] It is estimated that hypertension is controlled in only 54% of patients with the condition. Among children and adolescents (8 to 17 years old) 11% have high blood pressure or borderline high blood pressure. In 2013, approximately 1 of every 3 deaths in America was due to cardiovascular causes, and cardiovascular operations and procedures increased by 28% from 2000 to 2010. Hypertension is an independent risk factor for the development of cardiovascular disease (CVD).[32] The more elevated the blood pressure, the higher the risk of myocardial infarction (MI), stroke, heart failure (HF), and kidney disease.[33] To reduce the risk of cardiovascular (CV) events, the current recommended goal blood pressure is < 140/90 mm Hg.[34]

The American Diabetes Association (ADA) suggests that the blood pressure goal for many people with diabetes and hypertension should be < 140 mm Hg systolic and < 90 mm Hg diastolic, but that lower systolic and diastolic targets (such as < 130 mm Hg and < 80 mm Hg, respectively) may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden.[35] According to the National Kidney Foundation, for patients with chronic renal disease, the

current goal for blood pressure therapy is 130/80 mm Hg.[36] A consensus guideline by the American College of Cardiology (ACC), American Heart Associations (AHA) and other medical organizations recommend a target blood pressure of < 130/80 mm Hg for patients with known coronary artery disease (CAD) or CAD equivalent, stable angina, unstable angina (UA)/non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).[37] There is inter-patient variability in response to various antihypertensive classes. In the absence of compelling indications, reaching target blood pressure is central in determining CV benefit in patients with hypertension, not the specific agent used.[38,39,40]

The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) published evidence-based recommendations on the benefits and harms of higher (< 150 mmHg) versus lower (< 140 mmHg) systolic blood pressure (SBP) targets in the treatment of hypertensive adults ages 60 years and older.[41] The ACP and AAFP recommend initiating antihypertensive therapy in adults 60 years and older with SBP ≥ 150 mmHg with a target SBP < 150 mmHg to reduce the risk of mortality, stroke, and cardiac events (strong recommendation, high-quality evidence). A stricter goal of SBP < 140 mmHg may be considered in older adults with a history of stroke or transient ischemic attack to reduce the risk for recurrent stroke (weak recommendation, moderate-quality evidence). A stricter goal, SBP < 140 mmHg, may also be considered in older adults at high cardiovascular (CV) risk to reduce the risk of stroke or cardiac events (weak recommendation, moderate-quality evidence). The clinician and patient should discuss the risk versus benefit when determining the most appropriate blood pressure goal. The ACP and AAFP also state that providers should consider treatment with nonpharmacological options (e.g., weight loss, diet, exercise), as well as pharmacologic therapy. Also in support on non-pharmacologic options, the 2014 hypertension science advisory by the AHA, ACC, and Centers for Disease Control and Prevention (CDC) recommend that lifestyle modifications should be initiated in all patients with hypertension. Treatment burden (e.g., total number of drugs prescribed, drug interactions, adverse effects), given the potential for other comorbid conditions, should also be taken into consideration when treating hypertensive older adults. If pharmacologic therapy is chosen, generic formulations should be prescribed when available to reduce cost and thereby aid treatment adherence. For patients with certain co-morbid conditions, specific medications should be considered first-line treatments; beta-blockers are one of the classes suggested in patients with coronary artery disease, post-MI, HF, and diabetes. [42]

Most beta-blockers are indicated for the treatment of HTN with similar efficacy between the agents.[43,44,45,46] The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8), published in 2014, recommends first-line therapy for HTN in the non-African American population as a thiazide-type diuretic, CCBs, ACE inhibitors, or angiotensin receptor blocker (ARB) and a thiazide diuretic or CCB in the African American population. JNC-8 does not recommend beta-blockers as initial treatment of hypertension due to a demonstrated higher rate of the primary composite outcome of CV death, MI, or stroke compared to use of an ARB with their use, a finding that was driven largely by an increase in stroke.[47]

The role of beta-blockers as initial therapy, particularly in the absence of compelling indications, for hypertension has been questioned.[48] Beta-blockers have demonstrated similar efficacy in MI patients versus placebo or other drugs and reduced risk of stroke compared to placebo; however, beta-blockers are less effective than other antihypertensive drugs against stroke, particularly in the elderly.[49,50,51] Cochrane database reviews showed beta-blockers to be inferior to CCBs for all-cause mortality, stroke, and total CV events and to be inferior to ACE inhibitors and ARBs for stroke. Beta-blockers as first-line

for hypertension have also been shown to be inferior to low-dose thiazides, in reducing coronary heart disease and mortality.[52,53] It should be noted that the majority of the data are from trials involving atenolol.

A number of trials, including STOP-Hypertension-2, NORDIL, and INVEST, showed little difference in overall outcomes for beta-blockers and diuretics versus ACE inhibitors and CCBs.[54,55,56] The ASCOT-BPLA and LIFE trials showed that the beta-blocker atenolol had an increased rate of CVD and death compared to the CCB amlodipine.[57,58]

A recent Cochrane systematic review sought to quantify the dose-related blood pressure lowering effect of beta-1 selective blockers in patients with primary HTN.[59] A total of 56 randomized controlled trials were selected for review (total patients = 7,812) and results indicated that in patients with mild to moderate HTN, beta-1 selective agents significantly reduced both systolic blood pressure (SBP) and diastolic blood pressure (DBP). On an average, blood pressure lowering of 10/8 mm Hg and heart rate lowering of 11 beats per minute was reported.

Fixed-dose combinations of beta-blockers and diuretics are available. A meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attack, stroke, and death in patients taking HCTZ has been published.[60] Based on 14 studies, including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as ACE inhibitors, ARBs, beta-blockers, and calcium antagonists. Additionally, the meta-analysis concluded that there are no studies or evidence that HCTZ reduces myocardial infarction, stroke, or death.

African American patients generally have a suboptimal response to beta-blockers in blood pressure reduction compared to diuretics and CCBs; however, they still benefit from the reduction of risk from clinical outcomes when the same blood pressure reduction is achieved. Nebivolol has shown efficacy in reducing blood pressure in African Americans.[61]

It is estimated that 3.5% of children and adolescents have hypertension.[62] In 2017, American Academy of Pediatrics (APP) published guidelines on diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. The goal of treatment is to achieve a blood pressure that decreases the risk for organ damage in youth and decrease the risk of hypertension in adulthood. For children and adolescents on treatment for HTN, the blood pressure goal is < 90th percentile and < 130/80 mmHg. Lifestyle modifications such as diet and physical exercise are recommended for the potential benefit to reduce blood pressure. First line therapy options include an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic; treatment should begin a low dosage and titrate as needed; a second agent may be added if needed. Beta-blockers are not recommended as initial pharmacologic treatment in children due to the side effect profile and following the therapy recommendations of beta-blockers in adults. Long-term studies on the safety of antihypertensive medications in children and their impact on future cardiovascular disease are limited.

Heart Failure

Beta-blockers have been shown to reduce mortality in patients with chronic heart failure (alternatives include thiazide diuretics, CCBs, ACE inhibitors, and ARBs).[63]

Heart failure (HF) affects 6.5 million patients in the U.S.[64] Despite combination therapy with ACE inhibitors, diuretics, and digoxin, 5-year mortality rates remain high. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the diagnosis and management of Heart Failure in the adult identify 4 stages of HF recognizing both the development and progression of

the disease.[65] Patients in stages A and B are considered at risk for HF. Stage C are patients with structural heart disease with reduced left ventricular ejection fraction (LVEF) with prior or current symptoms of HF. Stage D patients have refractory HF requiring specialized interventions. For patients in Stage A with hypertension, optimal blood pressure is 130/80 mmHg. For Stage B, beta-blockers and ACE inhibitors should be used in all patients with a recent history of MI regardless of EF or presence of HF. Beta-blockers and ACE inhibitors are also recommended in patients without a history of MI, with a reduced ejection fraction, and no HF symptoms. In 2016 and 2017 ACC/AHA/Heart Failure Society of America (HFSA) published 2 updates to the 2013 guidelines that focused on new pharmacological therapies and management for HF for treatment of Stage C patients.[66],[67] For Stage C, these guidelines recommend diuretics and salt restriction in patients with evidence of fluid retention, ACE inhibitors or ARB in all patients, unless contraindicated, an evidence-based beta-blocker (bisoprolol, carvedilol, or metoprolol succinate extended-release), and a diuretic as needed. An ARB may be used in ACE inhibitor-intolerant patients and is considered a reasonable alternative. If an ACE inhibitor or ARB is tolerated, switching to an angiotensin receptor-neprilysin inhibitor (ARNI; sacubitril/valsartan) is recommended to further reduce morbidity and mortality. For patients with heart rate ≥ 70 bpm on maximally tolerated beta-blocker dosage, ivabradine may be beneficial to reduce HF hospitalization.

The beta-blockers with the Food and Drug Administration (FDA)-approved indication for HF are metoprolol succinate extended-release (Toprol XL, Kapspargo Sprinkles), a beta1-selective (cardioselective) adrenergic antagonist, and carvedilol (Coreg, Coreg CR), a combined alpha-blocker and non-selective beta-blocker.[68,69,70] Bisoprolol is a cardioselective beta-blocker that has been studied in HF; however, bisoprolol is not FDA-approved for this indication.

Bisoprolol, metoprolol succinate ER, and carvedilol in addition to an ACE inhibitor have been shown to reduce symptoms of HF and improve clinical status and patients' well-being plus reduce the risk of death and the combined risk of death and hospitalization.[71] All 3 drugs have been shown to reduce mortality and hospitalization by 30 to 40%, in HF.[72,73,74,75,76,77] There have been many placebo-controlled trials of beta-blockers in patients with systolic dysfunction already treated with the standard therapy of diuretics and ACE inhibitors. The COMET trial showed reduced mortality and vascular events with carvedilol versus metoprolol.[78,79]

Angina Pectoris

The American College of Cardiology/American Heart Association (ACC/AHA) chronic stable angina 2007 focused update of the original 2002 guidelines recommend beta-blockers and/or ACE inhibitors with the addition of other drugs, as needed, for blood pressure control in patients with CAD.[80] The 2007 guidelines recommend initiating and continuing beta-blocker therapy indefinitely in all patients who have had MI, acute coronary syndrome (ACS), or left ventricular dysfunction (LVD), with or without heart failure symptoms, unless contraindicated.

Beta-blockers appear to have similar efficacy in stable angina. Beta-1 selective agents without intrinsic sympathomimetic activity (ISA) are used most frequently.[81] Beta-blockers are able to improve exercise capacity and decrease frequency of angina episodes.[82] The cardioselective beta-blockers block the beta-1 receptor and have less inhibition of the peripheral vasodilation and bronchodilation induced by the beta-2 receptors. At higher doses, cardioselectivity may be lost. Beta-blockers with ISA may not decrease heart rate and blood pressure at rest, so these agents should be avoided in patients with a prior MI or HF who benefit from beta blockade. However, since it is the reduction in exercise heart rate that is of primary importance, the ISA beta-blockers can still be effective.

Acute MI (UA/NSTEMI and STEMI)

Beta-blockers prevent recurrent ischemia, life-threatening ventricular arrhythmias, and improve survival in patients with prior MI.[83,84] Unless contraindicated, the 2014 ACC/AHA guidelines for Non-ST Coronary Syndromes and the American College of Cardiology Foundation (ACCF)/AHA 2013 STEMI guidelines recommend indefinite beta-blocker therapy in all patients with UA and NSTEMI, collectively referred to as non-ST elevation ACS, and STEMI.[85,86] The 2014 AHA scientific statement on the treatment of hypertension in ischemic heart disease support these recommendations in hemodynamically-stable patients and prefer use of cardioselective beta-blockers without ISA.[87]

Cardiac Arrhythmia

Patients with arrhythmia have a higher risk of total mortality, coronary heart disease mortality, and sudden cardiac death.[88] Ventricular arrhythmias can occur in patients with heart failure, as well as with MI.[89,90,91] Ventricular arrhythmias contribute to the increased risk for sudden cardiac death in patients with HF and MI.[92,93,94,95,96] Beta-blockers improve survival in patients who have had a MI as they are able to reduce the incidence of sudden cardiac death.[97,98] The ACC/AHA/European Society of Cardiology (ESC) 2006 guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death consider beta-blockers to be safe and effective and the mainstay of antiarrhythmic drug therapy.[99]

In 2017, the American College of Cardiology (ACC) published new guidelines on syncope management.[100] Beta-blockers are recommended as first-line for long-QT syndrome (LQTS) and suspected arrhythmic syncope, if no contraindications. Beta-blockers that lack intrinsic sympathomimetic activity are recommended with catecholaminergic polymorphic ventricular tachycardia (CPVT) and stress-induced syncope. Beta-blockers might be reasonable in patients 42 years or older with recurrent vasovagal syncope (VVS). If syncope continues, flecainide, verapamil, fludrocortisone, midodrine, droxidopa, pyridostigmine, octreotide, or selective serotonin reuptake inhibitors (SSRI) may be options in select patients.

PHARMACOLOGY[101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125]

Beta-blockers are able to improve exercise capacity, decrease frequency of angina episodes, and reduce exercise-induced ST depression. The beneficial effect of beta-blockers in post-MI patients is related to resting heart rate reduction.[126] Beta-blockers inhibit the adverse effects of the sympathetic nervous system (SNS) in heart failure patients. Although cardiac adrenergic drive initially supports the performance of the failing heart, long-term activation of the SNS exerts deleterious effects. These effects include increased ventricular volumes and pressures, cardiac hypertrophy, provocation of arrhythmias, and apoptosis. Beta-blockers antagonize SNS activation, minimize damage, and, ultimately, slow disease progression.

The catecholamines, norepinephrine and epinephrine, are mediated by beta and alpha receptors. Beta-blockers bind to adrenergic receptors to competitively inhibit catecholamines, resulting in inhibition of vasoconstriction, chronotropic, and inotropic activity. Cardioselective beta-blockers are beta-1 selective resulting in decreased heart rate and contractility. Nonselective beta-blockers have equal affinity for both beta-1 and beta-2 receptors. Inhibition of beta-2 receptors causes bronchoconstriction and vasoconstriction. At higher doses, cardioselective agents can also block beta-2 adrenergic

receptors. Nebivolol (Bystolic) is beta-1 selective at doses ≤ 10 mg or in extensive metabolizers (majority of the population), but it loses cardioselectivity at doses above 10 mg and in poor metabolizers. Beta-blockers with alpha-adrenergic activity block alpha-1 receptors resulting in decreased peripheral and coronary vascular resistance. Beta-blockers with intrinsic sympathomimetic activity, also called partial agonist activity, have low-grade beta stimulation at rest.

Intrinsic sympathomimetic activity (ISA) characterizes a group of beta-blockers that are able to stimulate beta-adrenergic receptors (agonist effect) and to oppose the stimulating effects of catecholamines (antagonist effect) in a competitive way. The presence of ISA results in less resting bradycardia and less reduction in cardiac output than is observed with beta-blockers without ISA.[127]

Beta-blockers are available as fixed-dose combinations with thiazide and thiazide-like diuretics. The thiazide (bendroflumethiazide, hydrochlorothiazide) and thiazide-like diuretics (chlorthalidone) block the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume. Consequently, there are increases in plasma renin activity and aldosterone secretion. Concurrent administration of an angiotensin II receptor antagonist and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.[128,129]

Pharmacologic Properties

Drug	Cardioselective	ISA	Vasodilatory
acebutolol	Y	Y	--
atenolol	Y	--	--
betaxolol	Y	--	--
bisoprolol	Y	--	--
carvedilol	--	--	Y (alpha-1 antagonist)
carvedilol CR (Coreg CR)	--	--	Y (alpha-1 antagonist)
labetalol	--	--	Y (alpha-1 antagonist)
metoprolol tartrate	Y	--	--
metoprolol succinate ER	Y	--	--
nadolol	--	--	--
nebivolol (Bystolic)	Y	--	Y (nitric oxide pathway)
pindolol	--	Y	--
propranolol	--	--	--
propranolol ER (Innopran XL)	--	--	--
propranolol ER (Inderal XL)	--	--	--
propranolol LA	--	--	--
sotalol	--	--	--
sotalol AF	--	--	--
timolol	--	--	--

PHARMACOKINETICS[130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154]

Drug	Bioavailability (%)	Half-life (hrs)*	Metabolism	Excretion (%)
acebutolol	40	3-4	1 active metabolite (diacetolol)	Urine: 30-40
atenolol	50	6-7	Negligible hepatic metabolism	Urine: 50
betaxolol	89	14-22	Inactive metabolites	Urine
bisoprolol	80	9-12	Inactive metabolites	Urine
carvedilol	25-35 (Cmax reduced in presence of food)†	7-10	3 weakly active metabolites via CYP2D6 and CYP2C9	Primarily Feces
carvedilol CR (Coreg CR)	25-35 (Cmax reduced in the fasting state)‡	5-11	3 weakly active metabolites via CYP2D6 and CYP2C9	Primarily Feces; less than 7% in the urine
labetalol	25	6-8	Hepatic via glucuronidation	Urine: 55-60 as glucuronide conjugates
metoprolol succinate/ER	50	3-7	Inactive metabolites via CYP2D6	Predominantly urine
nadolol	30	20-24	None	Urine
nebivolol (Bystolic)	12-96	12-19	Hepatic: active metabolites via CYP2D6 and glucuronidation	Urine: 38 Feces: 44
pindolol	--	3-4	Hepatic (60%) to metabolites	Urine: 35-40 Feces: 6-9
propranolol	30-40	3-6	4 active metabolites via CYP2D6 and CYP1A2	Urine: 96-99
propranolol ER (Innopran XL)	25	8-11	4 active metabolites via CYP2D6 and CYP1A2	Urine
propranolol ER (Inderal XL)	25	8	4 active metabolites via CYP2D6 and CYP1A2	Urine
propranolol LA	25	8-11	4 active metabolites via CYP2D6 and CYP1A2	Urine
sotalol/AF	90-100	12	None	Urine
timolol	50	4	Hepatic to inactive metabolites	Urine

* Half-life of beta-blockers does not directly correlate with the duration of activity.

† Because the presence of food in the gut reduces the maximum concentration (Cmax) of carvedilol, it is recommended that this drug be taken with food to minimize the risk for hypotension.

‡ The AUC and Cmax of carvedilol controlled-release (Coreg CR) are decreased when given in a fasting state; therefore, carvedilol controlled-release (Coreg CR) should be administered with food to enhance absorption.

**At steady state, bioavailability of metoprolol succinate ER tablets and capsules is approximately 77% of the corresponding dose of IR tablets (with comparable beta blockade over the 24 hour dosing interval). At steady state, bioavailability of metoprolol succinate ER sprinkle capsules is reduced by 25% relative to the corresponding IR tablet dose.

Metabolizers of CYP2D6 (e.g., carvedilol, metoprolol, nebivolol, and propranolol) are subject to the effects of genetic polymorphism. The majority of the population is extensive metabolizers (EMs) and a

minority is poor metabolizers (PMs) of CYP2D6. Poor metabolizers exhibit higher plasma concentrations compared to extensive metabolizers.

CONTRAINDICATIONS/WARNINGS[155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179]

Abrupt discontinuation of or hypersensitivity to beta-blocker therapy, acute bronchospasm, cardiogenic shock, sick sinus syndrome (unless a permanent pacemaker is in place), advanced (greater than first degree) atrioventricular (AV) block, severe bradycardia, decompensated cardiac failure, anuria, and acute pulmonary edema are considered contraindications for use of beta-blockers.

In general, patients with bronchospastic diseases should not receive beta-blockers. Carvedilol, propranolol, and sotalol, are contraindicated in patients with asthma and related bronchospastic conditions. Metoprolol succinate ER may be used with extreme caution in patients with bronchospastic disease, such as asthma, who do not respond or cannot tolerate other antihypertensives. Since beta1-selectivity is not absolute, a beta2-stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol succinate ER should be used.

A Cochrane systematic review found that cardioselective beta-blockers in patients with chronic obstructive pulmonary disease (COPD) were not associated with respiratory adverse effects.[180] It should be noted that several of the included studies were single-dose studies or for short durations.

In diabetic patients, beta-blockers can mask some of the symptoms of hypoglycemia, particularly tachycardia. Other symptoms of hypoglycemia, such as dizziness or sweating, may not be significantly affected by beta-blocker therapy.

Patients with peripheral arterial disease (PAD) may experience worsening of symptoms on beta-blocker therapy. Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism, such as tachycardia. Abrupt beta-blocker withdrawal may be associated with an exacerbation of symptoms of hyperthyroidism and may precipitate thyroid storm.

Initiation of high-dose metoprolol extended-release should be avoided in patients undergoing non-cardiac surgery; use in patients with CV risk factors has been associated with bradycardia, hypotension, stroke, and death. Chronic beta-blocker therapy should not be routinely withdrawn prior to major surgery. However, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Caution should be exercised when amide anesthetics (e.g., lidocaine, bupivacaine, mepivacaine) are administered concomitantly with propranolol.

Beta-blockers should generally be avoided in vasospastic (Prinzmetal's) angina. In patients with pheochromocytoma, an alpha-blocking agent should be initiated prior to the use of any beta-blocker.

Propranolol (Hemangeol) oral solution is contraindicated in premature infants with corrected age less than 5 weeks and in infants weighing less than 2 kg. Do not use Hemangeol in patients who are not able to feed or are vomiting.

Sotalol is contraindicated in congenital or acquired long QT syndromes, baseline QT interval > 450 msec, cardiogenic shock, hypokalemia (< 4 mEq/L), or creatinine clearance < 40 mL/min.

Sotalol can cause serious ventricular arrhythmias, primarily Torsades de Pointes (TdP) type ventricular tachycardia, associated with QT interval prolongation. QT interval prolongation is directly related to the dose of sotalol. Factors such as reduced creatinine clearance, gender (female), and larger doses increase the risk of TdP. The risk of TdP can be reduced by adjustment of the sotalol dose according to creatinine clearance and by monitoring the ECG for excessive increases in the QT interval.

In single-dose studies, patients with cirrhosis have been reported to have significantly higher concentrations of carvedilol (4- to 7-fold) compared to healthy patients. Patients with severe liver disease should not receive carvedilol. Nebivolol (Bystolic) is contraindicated in severe hepatic impairment (Child-Pugh > B). Nebivolol should be used with caution in patients with moderate hepatic impairment. Propranolol, metoprolol, labetalol, acebutolol, and timolol should be used with caution in patients with impaired hepatic function. Bisoprolol should be used with caution in hepatic impairment and the dose adjusted. Pindolol should be used with caution in severe hepatic impairment and the dose adjusted. Thiazide diuretics should be used with caution in patients with impaired hepatic function, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Nebivolol should be used with caution in patients with severe renal impairment. Propranolol, nadolol, atenolol, and pindolol should be used with caution in patients with impaired renal function. Sotalol, acebutolol, and betaxolol should also be used with caution in patients with impaired renal function and the dose adjusted. Bisoprolol should be used with caution in patients with CrCl less than 40 mL/min and the dose adjusted. The dose of timolol should be adjusted in patients with CrCl < 10 mL/min. Thiazide diuretics are not recommended in patients when CrCl is ≤ 30 mL/min.

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers.

Hydrochlorothiazide has been reported to cause acute transient myopia and acute angle-closure glaucoma. Symptoms such as decreased visual acuity or ocular pain can occur within hours to weeks of drug initiation and, if untreated, can lead to permanent vision loss. Hydrochlorothiazide should be discontinued as rapidly as possible. Prompt medical or surgical treatments may be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

DRUG INTERACTIONS[181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205]

Concomitant use of beta-blockers and digitalis glycosides can increase the risk of bradycardia as both classes slow AV conduction and decrease heart rate. Amiodarone can increase beta-blocker levels; therefore, the combination should be used with caution. Co-administration of amiodarone and carvedilol has been shown to increase concentrations of the S-enantiomer of carvedilol by 2-fold. Therefore, patients should be observed for signs of bradycardia and heart block. Beta-blockers may potentiate rebound HTN after discontinuation of clonidine.

Verapamil and, to a lesser degree, diltiazem can potentiate the cardiac depressant effect of beta-blockers (potentially leading to bradycardia or heart block). Beta-blockers should be used with caution in combination with these agents.

The CYP2D6 enzyme is one of the enzymes that metabolize carvedilol, metoprolol, propranolol, timolol, and nebivolol (Bystolic). Strong inhibitors of CYP2D6, such as fluoxetine, quinidine, paroxetine, and propafenone, will cause the beta-blocker concentrations to increase. There will be an increased risk of adverse effects and a reduction in the cardioselectivity of metoprolol.

Beta-blockers, when given with catecholamine-depleting drugs such as monoamine oxidase (MAO) inhibitors and reserpine, may cause an exaggerated hypotensive response, such as vertigo, syncope, and postural hypotension. Monitoring for hypotension, bradycardia, vertigo, syncope, and postural hypotension should be performed. Concurrent administration with clonidine has been reported to potentiate the hypotensive effects and worsening of bradycardia.

Cyclosporine levels have been reported to increase with concurrent carvedilol therapy. Monitoring of cyclosporine levels and possible reduction in the cyclosporine dosage may be necessary.

Rifampin, a strong CYP 450 enzyme inducer, has been reported to reduce the bioavailability of carvedilol by 70%.

Sotalol/AF can increase levels of adenosine and other antiarrhythmic agents. The combination of diuretics and sotalol should be used with caution due to electrolyte imbalance.

Beta-blockers should not be used with the diagnostic agent, methacholine.

In the presence of alcohol, metoprolol succinate is released faster from the sprinkle formulation (Kapspargo). Therefore, alcohol consumption should be avoided with this product.

ADVERSE EFFECTS[206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230]

Adverse effects in HTN patients, and for sotalol/AF in ventricular tachycardia/ventricular fibrillation patients, are listed below.

Drug	Hypotension/ Postural Hypotension	Syncope	Dizziness/Vertigo	Bradycardia
acebutolol	2	nr	6	2
atenolol	2-4	reported	2-13	3
betaxolol	reported	< 2	4.5-14.8	5.8-8.1
bisoprolol	reported	reported	2.9-3.5	0.4-0.5
carvedilol (Coreg, Coreg CR)	2	reported	5	2
labetalol	1	reported	11	0
metoprolol succinate/ER (Toprol XL, Kapspargo Sprinkles)	reported	reported	>2 (includes angina patients)	>2 (includes angina patients)
metoprolol tartrate	0.1	0.1	0.1	0.3
nadolol	0.1	nr	0.2	0.2

Adverse Effects (continued)

Drug	Hypotension/ Postural Hypotension	Syncope	Dizziness/Vertigo	Bradycardia
nebivolol (Bystolic)	nr	reported	2-4	0-1
pindolol	reported	nr	reported	reported
propranolol/LA	reported	nr	reported	reported
propranolol ER (Innopran XL)	reported	nr	4-7	reported
propranolol ER (Inderal XL)	reported	nr	4-7	reported
sotalol/AF	reported-6	reported-5	13.1-20	12.3-16
timolol	reported	nr	reported	reported

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. nr = not reported

Sotalol/AF can cause serious ventricular arrhythmias, primarily Torsades de Pointes type ventricular tachycardia (associated with QT interval prolongation).

A meta-analysis of 15 trials with beta-blockers evaluated the risks of depression, fatigue, and sexual dysfunction.[231] For depressive symptoms, 7 trials with over 10,000 patients found there was no difference in the frequency of depressive symptoms in patients taking beta-blockers compared to those on placebo. In 10 trials with over 17,000 patients, fatigue was more frequently reported in patients taking beta-blockers. Older beta-blockers were more commonly associated with complaints of fatigue. In 6 trials with almost 15,000 patients, beta-blockers had slightly more reports of sexual dysfunction than placebo.

An overview of randomized beta-blocker trials quantified the risks of adverse effects in patients with HF.[232] Beta-blockers were associated with the increased risk of hypotension (11 per 1,000; 95% CI, 0 to 22), dizziness (57 per 1,000; 95% CI, 11 to 104), and bradycardia (38 per 1,000; 95% CI, 21 to 54). Fatigue was not associated with beta-blockers. Beta-blockers were associated with a reduction in all-cause withdrawal from therapy (14 per 1,000; 95% CI, -2 to 29), lower all-cause mortality (34 per 1,000; 95% CI, 20 to 49), HF hospitalizations (40 per 1,000; 95% CI, 22 to 58), and worsening HF (52 per 1,000; 95% CI, 10 to 94).

In clinical trials of primarily mild to moderate HF with immediate-release carvedilol, hypotension and postural hypotension occurred in 9.7% and syncope in 3.4% of patients compared to 3.6% and 2.5% of placebo patients, respectively. The risk for these events was highest during the first 30 days of dosing, corresponding to the up-titration period.[233]

In propranolol (Hemangeol) trials, the most frequently reported adverse events (occurring ≥ 10% of patients) were sleep disorders, aggravated respiratory tract infections, diarrhea, and vomiting.

SPECIAL POPULATIONS[234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252, 253,254,255,256,257,258]

Pediatrics

Safety and effectiveness of the beta-blockers in children have not been established, except for metoprolol ER (Toprol XL, Kapspargo Sprinkles) and propranolol (Hemangeol). Many of the agents have been used in children; however, clinical trial data are lacking. Safety and effectiveness of propranolol (Hemangeol) for infantile hemangioma have not been established in pediatric patients greater than 1 year of age.

In patients 6 years and older with hypertension, metoprolol succinate ER is given 1 mg/kg once daily. The maximum initial dose should not exceed 50 mg/day. The dose should be adjusted based on blood pressure response. Doses above 2 mg/kg/day or 200 mg/day have not been studied.

Pregnancy

Acebutolol, pindolol, and sotalol are Pregnancy Category B. Atenolol is Pregnancy Category D. The other beta-blockers in this review are Pregnancy Category C.

Other

Beta-blockers have been used for hypertension, but evidence for a benefit in the elderly has not been convincing. They may have a role in combination therapy, especially with diuretics. Beta-blockers are indicated in the treatment of elderly patients who have hypertension with CAD, HF, certain arrhythmias, migraine headaches, and senile tremor.[259] When switching elderly patients from higher doses of immediate-release carvedilol (12.5 mg or 25 mg twice daily) to controlled-release carvedilol (Coreg CR), a lower starting dose of controlled-release carvedilol should be considered to minimize the potential for syncope, dizziness, or hypotension.

Due to the increased risk of QT interval prolongation, treatment with sotalol/AF must be started only in patients observed for a minimum of 3 days on their maintenance dose in a facility that can provide electrocardiographic (ECG) monitoring and in the presence of personnel trained in the management of serious ventricular arrhythmias.

DOSAGES[260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282, 283,284]

Beta-Blockers: Single Agents

Drug	Hypertension	Angina Pectoris	Heart Failure	Other Indications	Availability
acebutolol (Sectral)	200–400 mg twice daily	-	-	See package insert for other indications	200 mg, 400 mg capsule
atenolol (Tenormin)	50–100 mg daily	50–200 mg daily	-	MI: 50 mg twice daily or 100 mg daily	25 mg, 50 mg, 100 mg tablets
betaxolol	10–20 mg daily	-	-	-	10 mg, 20 mg tablets

Dosages (continued)

Drug	Hypertension	Angina Pectoris	Heart Failure	Other Indications	Availability
bisoprolol	2.5–20 mg daily	-	-	-	5 mg, 10 mg tablets
carvedilol (Coreg)	6.25–25 mg twice daily	-	3.125–25 mg twice daily	LVD following MI: 3.125–25 mg twice daily	3.125 mg, 6.25 mg, 12.5 mg, 25 mg tablets
carvedilol CR (Coreg CR)	20–80 mg once daily	-	10–80 mg once daily	LVD following MI: 20–80 mg once daily	10 mg, 20 mg, 40 mg, 80 mg capsules
labetalol	100–400 mg twice daily	-	-	-	100 mg, 200 mg, 300 mg tablets
metoprolol succinate ER (Toprol XR, Kapspargo Sprinkle)	25–400 mg daily	100–400 mg daily	*12.5 - 200 mg daily	-	25 mg, 50 mg, 100 mg, 200 mg tablets and sprinkle capsules
metoprolol tartrate (Lopressor)	100–450 mg daily	50 mg twice daily to 400 mg daily	-	MI: 25–50 mg every 6 hours, then 100 mg twice daily	25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg tablets
nadolol (Corgard)	40–320 mg daily	40–240 mg daily	-	-	20 mg, 40 mg, 80 mg tablets
nebivolol (Bystolic)	5–40 mg daily	-	-	-	2.5 mg, 5 mg, 10 mg, 20 mg tablets

Dosages (continued)

Drug	Hypertension	Angina Pectoris	Heart Failure	Other Indications	Availability
pindolol	5 mg twice daily to 60 mg daily	-	-	-	5 mg, 10 mg tablets
propranolol	40 mg twice daily initially, then 120–240 mg/day in divided doses	80–320 mg daily in divided doses	-	See package insert for other indications	10 mg, 20 mg, 40, 60 mg, 80 mg tablets; 20 mg/5 mL, 40 mg/5 mL oral solution
propranolol (Hemangeol)	-	-	-	Infantile hemangioma: initiate at ages 5 weeks to 5 months at 0.15 mL/kg (0.6 mg/kg) twice daily; adjust to maintenance dose of 0.4 mL/kg (1.7 mg/kg) twice daily; administer at least 9 hours apart during or after feeding; monitor heart rate and blood pressure for 2 hours after the first dose or increasing dose	4.28 mg/mL oral solution (120 mL bottle)
propranolol ER (Innopran XL)	80 or 120 mg at bedtime	-	-	-	80 mg, 120 mg capsules
propranolol ER (Inderal XL)	80 or 120 mg at bedtime	-	-	-	80 mg, 120 mg capsules
propranolol LA (Inderal LA)	80 mg daily, then 120–160 mg daily	80–320 mg daily	-	See package insert for other indications	60 mg, 80 mg, 120 mg, 160 mg capsules
sotalol (Betapace)	-	-	-	See package insert for other indications	80 mg, 120 mg, 160 mg, 240 mg tablets
sotalol AF (Betapace AF)	-	-	-	See package insert for other indications	80 mg, 120 mg, 160 mg tablets
sotalol (Sotylize)	-	-	-	See package insert for other indications	5 mg/mL oral solution
timolol	10–30 mg twice daily	-	-	MI: 10 mg twice daily See package insert for other indications	5 mg, 10 mg, 20 mg tablets

Dosages (continued)

Combination Products

Drug	Initial Hypertension Dosage	Maximum Hypertension Dosage	Availability
atenolol / chlorthalidone (Tenoretic)	50/25 mg once daily	100/25 mg once daily	50/25 mg, 100/25 mg tablets
bisoprolol / hydrochlorothiazide (Ziac)	2.5/6.25 mg once daily	20/12.5 mg once daily	2.5/6.25 mg, 5/6.25 mg, 10/6.25 mg tablets
metoprolol succinate / hydrochlorothiazide (Dutoprol)	Individualized based on baseline and target blood pressure, as well as previous experience with antihypertensives	200/25 mg once daily (two 100/12.5 mg tablets)	25/12.5 mg, 50/12.5 mg, 100/12.5 mg tablets
metoprolol tartrate / hydrochlorothiazide	50/25 mg twice daily	100/25 mg given as 1–2 tablets in a single or divided doses 100/50 mg given a single dose	50/25 mg, 100/25 mg, 100/50 mg tablets
nadolol / bendroflumethiazide (Corzide)	40/5 mg once daily	80/5 mg once daily	40/5 mg, 80/5 mg tablets
propranolol / hydrochlorothiazide	40/25 mg twice daily	80/25 mg once or twice daily	40/25 mg, 80/25 mg tablets

*A starting dose metoprolol succinate ER sprinkle capsules (Kapspargo) is 25 mg once daily for 2 weeks; an initial therapy with < 25 mg daily, it not suitable for the sprinkle capsules.

For patients taking metoprolol succinate ER tablets (at a dose of 25 mg-200 mg daily), Kapspargo Sprinkle may be substituted for the tablets using the same total daily dose of metoprolol succinate. Kapspargo sprinkles can be swallowed whole, sprinkled over soft food, or administered via a nasogastric tube.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included all agents in this class for the cardiovascular (CV) FDA-approved indications of hypertension, HF, angina, MI, and cardiac arrhythmia and comparative studies of nebivolol to other beta-blockers for hypertension. Very few comparative clinical trials in HF have been performed with agents in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Angina

Head-to-head trials of FDA-approved beta-blockers for angina are lacking. Propranolol, which was the first beta-blocker, was shown to have efficacy in angina.[285] In very small trials, atenolol, metoprolol, and nadolol were shown to be as effective as propranolol in reducing anginal attacks and increasing exercise capacity.[286,287,288] Comparative studies of various beta-blockers have shown similar efficacy in angina.[289,290,291]

A double-blind, multicenter trial of 280 patients with stable angina randomized patients at week 0 to metoprolol controlled-release 200 mg once daily or nifedipine 20 mg twice daily for 6 weeks; placebo or the alternative drug was then added for a further 4 weeks.[292] Exercise tests at week 6 showed both metoprolol and nifedipine increased the mean exercise time to 1-mm ST segment depression in comparison with week 0 (both $p<0.01$). Metoprolol was more effective than nifedipine ($p<0.05$).

In a randomized, double-blind, 3-month, multicenter study, carvedilol 25 to 50 mg twice daily was compared to metoprolol 50 to 100 mg twice daily in 368 patients with stable angina for antianginal and anti-ischemic efficacy.[293] Carvedilol improved the time to 1-mm ST-segment depression statistically significantly greater than metoprolol. Carvedilol at both doses was shown to be at least as safe and well tolerated as metoprolol at both doses.

Cardiac Arrhythmia

Head-to-head trials of FDA-approved beta-blockers for ventricular arrhythmias are lacking. Studies of carvedilol, bisoprolol, atenolol, nadolol, pindolol, and metoprolol have shown efficacy in controlling ventricular rate.[294,295,296,297]

Sotalol (Betapace, Sotylize) has been found to be effective in ventricular arrhythmias.[298,299] Sotalol AF (Betapace AF) has been studied in patients with symptomatic atrial fibrillation/atrial flutter (primarily paroxysmal atrial fibrillation/atrial flutter and patients with chronic atrial fibrillation) in randomized, double-blind, multicenter, placebo-controlled trials. In the studies, sotalol/AF prolonged the time to first recurrence of ECG-documented symptomatic atrial fibrillation/atrial flutter, and reduced the risk of recurrence for up to 12 months.[300] Safety and effectiveness of Sotylize, the oral solution of sotalol, were based on oral sotalol tablets.

Heart Failure

carvedilol (Coreg) versus placebo

U.S. Carvedilol Heart Failure Study: A double-blind, placebo-controlled study (n=1,094) evaluated carvedilol use in HF.[301] The primary endpoint was all-cause mortality with a secondary endpoint of cardiovascular morbidity (hospitalization). The population was mostly men with ischemic heart disease, NYHA Class II and III, with a LVEF ≤ 35%. Therapy with ACE inhibitors and diuretics for at least 2 months was required for inclusion in the study. Carvedilol was initiated at 6.25 mg twice daily (open-label). If tolerated, patients were randomized to carvedilol 12.5 mg twice daily or placebo in a double-blind manner. The target doses of carvedilol were 25 to 50 mg twice daily for 6 to 12 months. The trial was stopped early due to the carvedilol group having a 65% lower relative risk of death than the placebo group ($p<0.001$). Carvedilol patients had a 27% relative risk reduction in hospitalization for cardiac reasons ($p=0.036$). Worsening of HF was the most common reason for withdrawal from the study and was seen more frequently in the placebo group.

carvedilol in severe HF (COPERNICUS): In a double-blind study evaluating the use of carvedilol in severe chronic HF, 2,289 patients with LVEF < 25% were randomized to carvedilol or placebo and evaluated for rates of hospitalizations and death.[302] Patients had symptoms at rest or with minimal exertion despite therapy with diuretics, ACE inhibitors, or ARBs. The carvedilol group had a 35% decrease in the relative risk of death over the placebo group in the mean 10.4-month study period (p=0.0014). The relative combined risk of death and hospitalization was reduced by 24% in the carvedilol group compared to the placebo group (p=0.00002). More patients withdrew from the study in the placebo group due to adverse effects or other reasons (p=0.02). An evaluation of carvedilol dose titration during the first 8 weeks of therapy did not demonstrate an increase, but rather a decrease of deaths, hospitalizations, and number of patients withdrawing from the study, as compared to placebo.[303] Worsening of HF was similar in both groups (carvedilol 5.1%, placebo 6.4%).

carvedilol (Coreg) after MI with LVD (CAPRICORN): A trial enrolling 1,959 patients evaluated carvedilol in the setting of acute MI complicated by LVD.[304] In the multicenter, double-blind, placebo-controlled trial, patients with MI and LVEF ≤ 40% were randomized to carvedilol 6.25 mg twice daily or placebo. The primary outcomes were all-cause mortality or hospital admission for cardiac reasons. Eligible patients were receiving ACE inhibitors and diuretics. Therapy was titrated to a maximum of carvedilol 25 mg twice daily over 4 to 6 weeks. The mean follow-up was 1.3 years. All-cause mortality was lower in the carvedilol group compared to placebo (12% carvedilol, 15% placebo, 23% relative risk reduction; p=0.03). Atrial and ventricular antiarrhythmic effects by carvedilol have been observed in this population.[305]

carvedilol (Coreg) versus metoprolol tartrate (Lopressor)

One hundred fifty patients with HF and LVEF <35% were randomized to double-blind treatment with either metoprolol or carvedilol.[306] When compared with metoprolol (average dose 124 ± 55 mg/day), patients treated with carvedilol (49 ± 18 mg/day) showed larger increases in LVEF at rest (+10.9% versus +7.2%, p=0.038) and in LV stroke volume and stroke work during exercise (both p<0.05) after 13- to 15-months of treatment. Carvedilol produced greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure, both at rest and during exercise, compared to metoprolol (all p<0.05). In contrast, the metoprolol group showed greater increases in maximal exercise capacity than the carvedilol group (p=0.035). Both drugs improved symptoms, submaximal exercise tolerance, and quality of life to a similar degree. After a mean of 23 months of follow-up, 21 patients in the metoprolol group and 17 patients in the carvedilol group died or underwent transplantation.

COMET was a randomized, double-blind trial comparing carvedilol and metoprolol tartrate in 3,029 patients with HF for effects on all-cause mortality.[307] Most patients were classified as NYHA Class II and III and were on diuretics, ACE inhibitors, or ARBs with optional treatment with digoxin and spironolactone. All patients had a history of a cardiovascular event within 2 previous years. The average LVEF was 26% at baseline. Baseline heart rates were identical between the groups. Patients were randomized to carvedilol 3.125 mg twice daily and titrated to 25 mg twice daily or metoprolol tartrate 5 mg twice daily and titrated to 50 mg twice daily. The target dose was achieved by 75% of carvedilol patients and 78% of metoprolol patients. The average daily dose was 42 mg for carvedilol and 85 mg for metoprolol tartrate. Patients were followed for a mean of 58 months. All-cause mortality was 34 and 40% for carvedilol and metoprolol tartrate, respectively (p=0.0017); COMET demonstrated a 17% relative risk reduction in all-cause mortality with carvedilol. The annual mortality rate was 8.3% for carvedilol group and 10% for metoprolol tartrate. The secondary endpoint of all-

cause mortality and all-cause hospitalization was similar between the 2 groups. Fewer carvedilol patients experienced cardiovascular death (p=0.0004).[308] After 4 months, carvedilol reduced heart rate by a mean of 13.3 beats per minute, whereas metoprolol reduced heart rate by 11.7 beats per minute. After 16 months, heart rate was similar between the groups. Overall, 32% of patients in both groups withdrew from the study. A criticism of the study is the lack of possible dose equivalency with carvedilol having a higher dose and lower heart rate therefore possibly greater benefits than metoprolol tartrate.

An analysis of the COMET trial compared the effects of carvedilol and metoprolol tartrate on vascular events.[309] Vascular endpoints were cardiovascular death, stroke, stroke death, myocardial infarction, and unstable angina. MI was seen in 69 carvedilol and 94 metoprolol patients (hazard ratio, 0.71; 95% CI, 0.52 to 0.97; p=0.03). Cardiovascular death and nonfatal MI combined were reduced by 19% in carvedilol versus metoprolol (hazard ratio, 0.81; 95% CI, 0.72 to 0.92; p=0.0009). Unstable angina was seen in 56 carvedilol-treated patients versus 77 metoprolol-treated patients (hazard ratio, 0.71; 95% CI, 0.501 to 0.998; p=0.049). Stroke was reported in 65 versus 80 patients receiving carvedilol and metoprolol, respectively (hazard ratio, 0.79; 95% CI, 0.57 to 1.1; p=0.163). Stroke or MI combined occurred in 130 carvedilol-treated and 168 metoprolol-treated patients (hazard ratio, 0.75; 95% CI, 0.6 to 0.95; p=0.015), and fatal MI or fatal stroke occurred in 34 patients on carvedilol versus 72 patients receiving metoprolol (hazard ratio, 0.46; 95% CI, 0.31 to 0.69; p=0.0002). The results show carvedilol improves vascular outcomes compared to metoprolol; however, the possible lack of dose equivalency in the COMET trial must be taken into account.

The objective of GEMINI, a randomized, double-blind, parallel-group trial, was to compare metoprolol tartrate and carvedilol in patients with diabetes.[310] A total of 1,235 patients with diabetes aged 36 to 85 years (mean age 61 years) were enrolled in GEMINI at 205 sites in the U.S. All participants in GEMINI had stage 1 or 2 HTN (systolic blood pressure, SBP, 130-179 mm Hg and diastolic blood pressure, DBP, 80-109 mm Hg), currently on an ACE inhibitor or ARB, and controlled type 2 diabetes (baseline glycosylated hemoglobin, HbA1c, 6.5 to 8.5% and C-peptide >0.6 ng/mL). There were no significant differences in baseline characteristics between the 2 groups. Less than 10% of patients had a history of coronary artery disease. Patients were randomized to carvedilol 6.25 mg twice daily (titrated to a maximum of 25 mg twice daily) or metoprolol tartrate 50 mg twice daily (titrated to maximum of 200 mg twice daily) and followed for a maximum of 35 weeks. Open-label hydrochlorothiazide 12.5 mg followed by a dihydropyridine CCB was added, if needed, to achieve blood pressure targets. The primary outcome was the mean change from baseline HbA1c following 5 months of maintenance therapy. Based on last observation carried forward, the carvedilol group had a significant change from baseline HbA1c (-0.12 percent; p=0.006). A greater proportion of subjects on metoprolol than on carvedilol had increases in HbA1c of greater than 0.5% (30% versus 22%, respectively) or greater than 1% (14.2% versus 7%, respectively). Since blood pressure control and mean heart rate use of antihypertensive and lipid-lowering medications were similar in the 2 treatment groups, the GEMINI investigators believe that these could not have accounted for differences in HbA1c. Subjects in the carvedilol group had improved insulin resistance, as measured by the homeostasis model assessment insulin resistance index (HOMA-IR) (p=0.04), and less microalbuminuria, as measured by urinary albumin/creatinine excretion rate, compared with the metoprolol group (p=0.003). Significantly fewer subjects on carvedilol developed new-onset microalbuminuria compared with those on metoprolol (6.6% versus 11.1%; odds ratio, 0.53; 95% CI, 0.3 to 0.93; p=0.05). The frequency of bradycardia was higher with metoprolol (p=0.007) which may be indicative of a lack of equivalent doses between the 2

agents. Diabetes worsened in more patients in the metoprolol group (p=0.07) with more patients withdrawing due to worsening glycemic control (p=0.04). Weight gain was higher with metoprolol (1.2 kg versus 0.2 kg, p<0.001).

metoprolol succinate ER (Toprol XL) versus placebo

MERIT-HF trial: A double-blind, placebo-controlled study enrolled 3,991 patients with chronic HF (NYHA Class II-IV and LVEF < 40%).[311] Patients were stabilized on optimal concomitant therapy including diuretics, ACE inhibitors, cardiac glycosides, and nitrates. At randomization, 41% of patients were NYHA Class II and 55% were NYHA Class III. Patients were started on 12.5 mg once daily of metoprolol succinate ER if NYHA Class III-IV or 25 mg once daily if NYHA Class II. Dose titration occurred over an 8-week period, if tolerated. The mean daily dose of metoprolol succinate ER at the end of the trial was 159 mg. The target dose of metoprolol succinate ER 200 mg daily was achieved in 64% of patients. The trial was terminated early (mean duration of 1 year) because of a 34% relative risk reduction in all-cause mortality.

Numerous subgroup analyses have found positive effects with metoprolol succinate ER in HF. In the MERIT-HF study, women (n=898) with NYHA III and IV were found to benefit from metoprolol succinate ER. A 21% relative risk reduction was noted in the combined endpoint of all-cause mortality and all-cause hospitalization for women (p=0.044).[312] The relative risk of hospitalization for worsening HF was also reduced by 42% in the metoprolol succinate ER group compared to placebo. The relative risk reduction in total mortality was also observed for hypertensive patients and for patients with severe HF randomized to metoprolol succinate ER.[313,314] In a sub analysis, metoprolol succinate ER provided benefits in African American patients with clinically stable HF and LVD.[315]

The REversal of Ventricular Remodeling with Toprol-XL (REVERT) trial: In a randomized, controlled study, 149 patients with LVEF < 40%, mild left ventricular dilation, and no symptoms of heart failure (NYHA class I) received metoprolol succinate ER 200 mg, 50 mg, or placebo for 12 months.[316] At 1 year, the metoprolol succinate ER 200 mg group showed a 14 +/- 3 mL/m^2 decrease (least square mean+/- SE) in end systolic volume index and a 6% +/-1% increase in left ventricular ejection fraction (p<0.05 versus baseline and placebo for both). In the metoprolol succinate ER 50 mg group, there were no statistical differences in end-systolic and end-diastolic volume indexes versus placebo; however, ejection fraction increased by 4% +/- 1% (p<0.05 versus baseline and placebo).

Hypertension

In the 1980s and 1990s, a number of head-to-head studies of beta-blockers found them to be similar in reducing blood pressure.[317,318,319,320,321] In addition, beta-blockers were compared to diuretics and were generally shown to be less effective in reducing cardiovascular events, as demonstrated in the MRC and HAPPHY trials.[322,323] The MAPHY trial, however, showed a lower all-cause mortality for metoprolol than a thiazide diuretic in relatively young white men aged 40 to 64 years old.[324] Beta-blockers have also been compared to other classes. The INVEST trial found atenolol and the calcium channel blocker verapamil to have the same effect on blood pressure reduction, and there was no difference in the primary endpoints.[325] More recently, there has been debate regarding the use of beta-blockers for primary prevention in hypertension.

Notable trials of special populations have also provided insight on the use of beta-blockers for the treatment of hypertension. While it has not been compared to other beta-blockers in this group, nebivolol has demonstrated a reduced blood pressure in African Americans, a population who typically

do not respond to beta-blockers, as well as Caucasians. [326] It has also demonstrated efficacy in other populations as well (e.g., Hispanics). [327] Additional trials have demonstrated the safety of metoprolol succinate ER in patients ≥ 6 years of age, a labeled use; however, not all trials have not consistently met predefined endpoints for target blood pressure reduction in this population.[328]

ASCOT-BPLA: The trial was a randomized controlled, multicenter, trial of 19,257 patients with hypertension aged 40 to 79 years with at least 3 other CV risk factors.[329] Amlodipine 5 to 10 mg (adding perindopril 4 to 8 mg, as required) or atenolol 50 to 100 mg (adding bendroflumethiazide 1.25 to 2.5 mg and potassium, as required) were evaluated for the primary endpoint of non-fatal MI and fatal CHD. The study was stopped early after 5.5 years of median follow-up. The amlodipine group was associated with greater reduction in all-cause mortality. The amlodipine group had lower risk of stroke (HR, 0.77; 95% CI, 0.66 to 0.89; p=0.0003) and improved survival (HR, 0.89; 95% CI, 0.81 to 0.99; p=0.0247) compared to the atenolol group. Cardiovascular mortality was also lower in the amlodipine group (HR, 0.76; 95% CI, 0.65 to 0.9; p=0.001). Fewer patients in the amlodipine group met the primary endpoint, but this was not a statistically significant difference (p=0.1052).

LIFE: The study was a randomized, double-blind, parallel-group study of 9,193 patients aged 55 to 80 years with essential hypertension and LVH.[330] Patients were randomized to once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years and until 1,040 patients had a primary cardiovascular event (death, MI, or stroke). Both treatments effectively lowered blood pressure. Losartan reduced the primary outcome (13% greater than atenolol) as there was a 25% relative risk reduction of stroke risk (absolute risk reduction 4%, 27.9% for atenolol and 23.8% for losartan, p=0.021).

nebivolol (Bystolic) versus atenolol

A 12-week, double-blind, randomized, multicenter study compared nebivolol to atenolol in 205 middle-aged patients with mild to moderate hypertension.[331] After a placebo run-in phase, patients received either nebivolol 5 mg daily or atenolol 100 mg daily. The primary endpoint of the study was the change in SBP and DBP from baseline. Both agents showed similar significant antihypertensive effects for SBP and DBP reduction ($p<0.01$ for all values). Sitting and standing heart rate values were significantly reduced by both agents. The bradycardic response induced by nebivolol treatment was significantly less than atenolol. Nebivolol demonstrated a better tolerability profile and a lower incidence of adverse effects.

A randomized, double-blind, parallel-group study compared once daily nebivolol 5 mg, atenolol 50 mg, and placebo in 366 patients with mild to moderate hypertension for 4 weeks.[332] There was a similar reduction in SBP and DBP compared to placebo for both agents. Both drugs were well tolerated.

A 9-month extension study of three, 3-month, phase 3 double-blind, randomized trials showed patients receiving nebivolol monotherapy had decreases in DBP and SBP of 15 and 14.8 mm Hg, respectively.[333] More than 78% of patients were responders to nebivolol monotherapy, and 65% were responders to combination with a diuretic. Overall incidence of adverse events in the extension study was comparable to that seen in the feeder studies and decreased over time.

Myocardial Infarction

Head-to-head trials of beta-blockers in MI are lacking. Placebo comparative trials are described below. The CAPRICORN study with carvedilol is discussed in the CHF section.[334]

metoprolol versus placebo

Goteborg: The Goteborg Metoprolol Trial, randomized 1,395 patients with suspected acute MI, on admission, to double-blind treatment with placebo or metoprolol (15 mg IV followed by 200 mg orally daily) for 90 days. Deaths occurred in 8.9% of placebo and 5.7% of metoprolol groups, a mortality reduction of 36% ($p<0.03$). After 90 days, all patients were recommended open treatment with metoprolol, and the difference in mortality between the 2 groups was maintained after 1 year. Early institution (within 12 hours) of metoprolol influenced infarct development during the first 3 days. Metoprolol reduced the incidence on fatal and nonfatal infarction by 35%, during the next 4 to 90 days. Fewer episodes of ventricular fibrillation were recorded in the metoprolol group versus placebo (6 versus 17 patients). Therapies were well tolerated. A retrospective subgroup analysis of Goteborg found that, during the first year, mortality in the metoprolol group was 14% versus 27% among patients randomized to placebo ($p=0.0099$).[335] Patients randomized to placebo who showed signs of heart failure had a 1 year mortality rate of 28% compared with 10% for patients without signs of heart failure ($p<0.001$).

MIAMI: MIAMI was a randomized, double-blind, multicenter study of 5,778 patients with definite or suspected MI, evaluating the effect of metoprolol on mortality and morbidity.[336] Metoprolol (15 mg IV followed by 200 mg/day orally) or placebo was started shortly after the patient's arrival in hospital within 24 hours of the onset of symptoms, and continued for the study period (15 days). There was a 13% nonsignificant difference in the incidence of death between metoprolol and placebo ($p=0.29$). Metoprolol seemed to have most effect on mortality in patients with multiple risk factors who were at higher risk, when previously recorded risk indicators of mortality were retrospectively analyzed. These indicated that there was a category which showed higher risk which contained approximately 30% of all randomized patients. In these, the mortality rate in the metoprolol-treated group was 29% less than in the placebo group. In the remaining lower risk categories, there was no difference between the treatment groups. There was no significant effect on ventricular fibrillation, but the number of episodes was lower in the metoprolol group during days 6 through 15. The incidence of supraventricular tachyarrhythmias, the use of cardiac glycosides and other antiarrhythmics, and the need for pain-relieving treatment were significantly diminished by metoprolol amongst all randomized patients. Treatments were well tolerated.

timolol versus placebo

Norwegian Multicenter Study: A randomized, double-blind, placebo-controlled, multicenter study compared timolol 10 mg twice daily with placebo for reduction in mortality and reinfarction.[337] Treatment was started 7 to 28 days after infarction in 1,884 patients and followed for a mean of 17 months. When deaths that occurred during treatment or within 28 days of withdrawal were considered, the cumulated sudden-death rate over 33 months was 13.9% in placebo versus 7.7% in the timolol group, a reduction of 44.6% ($p=0.0001$). The cumulated reinfarction rate was 20.1% in placebo and 14.4% in the timolol group ($p=0.0006$). A 6-year follow-up showed a cumulative mortality rate of 32.3% in placebo and 26.4% in the timolol group ($p=0.0028$).[338]

propranolol versus placebo

BHAT: The beta-Blocker Heart Attack Trial (BHAT) was a randomized, double-blind, placebo-controlled, multicenter study.[339] The primary endpoint was reduction in total mortality during a 2- to 4-year

period. BHAT randomized 3,837 patients with a prior MI to either propranolol or placebo, 5 to 21 days after the infarction. Depending on serum drug levels, the dose of propranolol was either 180 or 240 mg/day. The trial was stopped 9 months early. Total mortality during the average 24-month follow-up period was 7.2% in the propranolol group and 9.8% in the placebo group. Arteriosclerotic heart disease (ASHD) mortality was 6.2% in the propranolol group and 8.5% in the placebo group. Sudden cardiac death, a subset of ASHD mortality, was 3.3% among the propranolol patients and 4.6% among the placebo patients. Serious adverse effects were uncommon. A retrospective subgroup analysis of BHAT found that the incidence of heart failure after randomization and during the study was 6.7% in both groups so heart failure did not change propranolol's effect on total mortality.[340]

META-ANALYSIS

A systematic review between January 1966 and January 1998 identified 10 trials involving a total of 16,164 hypertensive elderly patients (≥ 60 years) and assessed antihypertensive efficacy of beta-blockers (mostly atenolol trials) and their effects on CV morbidity and mortality and all-cause morbidity compared with diuretics.[341] Diuretic therapy was superior to beta-blockade with regard to all endpoints and was effective in preventing cerebrovascular events (OR, 0.61; 95% CI, 0.51 to 0.72), fatal stroke (OR, 0.67; 95% CI, 0.49 to 0.9), CHD (OR, 0.74; 95% CI, 0.64 to 0.85), CV mortality (OR, 0.75; 95% CI, 0.64 to 0.87), and all-cause mortality (OR, 0.86; 95% CI, 0.77 to 0.96). In contrast, beta-blocker therapy only reduced the odds for cerebrovascular events (OR, 0.75; 95% CI, 0.57 to 0.98) but was ineffective in preventing CHD, CV mortality, and all-cause mortality (ORs, 1.01, 0.98, and 1.05, respectively).

A meta-analysis evaluated the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension in 17,671 patients.[342] Four studies that compared atenolol with placebo or no treatment, and 5 that compared atenolol with other antihypertensive drugs (half from the LIFE study) were identified. Despite major differences in blood pressure lowering, there were no outcome differences between atenolol and placebo in the 4 studies, on all-cause mortality (relative risk 1.01 [95% CI, 0.89 to 1.15]), cardiovascular mortality (0.99 [0.83 to 1.18]), or MI (0.99 [0.83 to 1.19]). The risk of stroke, however, tended to be lower in the atenolol group than in the placebo group (0.85 [0.72 to 1.01]). When atenolol was compared with other antihypertensives, there were no major differences in blood pressure reduction between the treatment arms. There was a significantly higher all-cause mortality (1.13 [1.02 to 1.25]) with atenolol than with other active treatment. Stroke was also more frequent with atenolol treatment (relative risk 1.3).

A meta-analysis of 13 randomized controlled trials compared primary prevention of beta-blockers to other antihypertensive classes, in 105,951 patients.[343] The relative risk of stroke was 16% higher for beta-blockers (95% CI, 4 to 30) than for other agents. There was no difference for MI. Beta-blockers did reduce the risk of stroke compared with placebo or no treatment; the relative risk of stroke was reduced by 19% for all beta-blockers (7% to 29%), which is about half that expected from prior hypertension trials. There was no difference for MI or mortality. A re-analysis of this meta-analysis, and when more trials were included, in older patients (≥ 60 years) beta-blockers had a higher risk of stroke (RR, 1.18; 95% CI 1.07 to 1.3) compared to other drugs.[344] There were no differences between beta-blockers and other drug classes in younger patients (< 60 years) in the composite outcome of death, MI, or stroke).

A Cochrane database systematic review included 13 randomized controlled trials of 91,561 patients and compared beta-blockers to placebo or no treatment (4 trials with 23,613 patients), diuretics (5

trials with 18,241 patients), calcium-channel blockers (CCB) (4 trials with 44,825 patients), and renin-angiotensin system (RAS) inhibitors (3 trials with 10,828 patients).[345] The risk of all-cause mortality was not different between first-line beta-blockers and placebo, diuretics, or RAS inhibitors, but was higher for beta-blockers compared to CCBs (RR, 1.07; 95% CI, 1 to 1.14). The risk of total cardiovascular disease (CVD) was lower for first-line beta-blockers compared to placebo (RR, 0.88; 95% CI, 0.79 to 0.97). This is due to the significant decrease in stroke (RR, 0.8; 95% CI, 0.66 to 0.96); coronary heart disease (CHD) risk was not significantly different between beta-blockers and placebo. The effect of beta-blockers on CVD was significantly compared to CCBs (RR, 1.18; 95% CI, 1.08 to 1.29), but was not significantly different from diuretics or RAS inhibitors. Increased total CVD was due to an increase in stroke versus CCBs (RR, 1.24; 95% CI, 1.11 to 1.4).There was also an increase in stroke with beta-blockers compared to RAS inhibitors (RR, 1.3; 95% CI, 1.11 to 1.53). There was no significant difference in CHD between beta-blockers and diuretics or CCBs or RAS inhibitors. Patients on beta-blockers were more likely to discontinue treatment due to adverse events than with diuretics (RR, 1.86; 95% CI, 1.39 to 2.5) and RAS inhibitors (RR, 1.41; 95% CI, 1.29 to 1.54), but there was no significant difference with CCBs. Seventy five percent of patients in these studies used atenolol. Differential effects on age or race were not explored.

A Cochrane database systematic review included 24 randomized trials (n=58,040) of at least 1 year duration comparing 1 of 6 major drug classes with a placebo or no treatment.[346] Thiazides (19 RCTs) reduced mortality (RR, 0.89; 95% CI, 0.83 to 0.96), stroke (RR, 0.63; 95% CI, 0.57 to 0.71), CHD (RR, 0.84; 95% CI, 0.75 to 0.95), and CV events (RR, 0.7; 95% CI, 0.66 to 0.76). Low-dose thiazides (8 RCTs) reduced CHD (RR, 0.72; 95% CI, 0.61 to 0.84), but high-dose thiazides (11 RCTs) did not (RR, 1.01; 95% CI, 0.85 to 1.2). Beta-blockers (5 RCTs) reduced stroke (RR, 0.83; 95% CI, 0.72 to 0.97) and CV events (RR, 0.89; 95% CI, 0.81 to 0.98), but not CHD (RR, 0.9; 95% CI, 0.78 to 1.03) or mortality (RR, 0.96; 95% CI, 0.86 to 1.07). ACE inhibitors (3 RCTs) reduced mortality (RR, 0.83; 95% CI, 0.72 to 0.95), stroke (RR, 0.65; 95% CI, 0.52 to 0.82), CHD (RR, 0.81; 95% CI, 0.7 to 0.94), and CV events (RR, 0.76; 95% CI, 0.67 to 0.85). CCBs (1 RCT) reduced stroke (RR, 0.58; 95% CI, 0.41 to 0.84) and CV events (RR, 0.71; 95% CI, 0.57 to 0.87), but not CHD (RR, 0.77; 95% CI, 0.55 to 1.09) or mortality (RR, 0.86; 95% CI, 0.68 to 1.09). No RCTs were found for ARBs or alpha-blockers.

A meta-analysis of 9 studies evaluated the effect of heart rate reduction on CV outcomes in 34,096 patients with hypertension with a mean age of 58 years.[347] Paradoxically, the slower the heart rate the greater the risk of CV outcomes and death. A lower heart rate was associated with a greater risk for the endpoints of all-cause mortality (r=-0.51; p<0.0001), cardiovascular mortality (r=-0.61; p<0.0001), myocardial infarction (r=-0.85; p<0.0001), stroke (r=-0.2; p=0.06), or heart failure (r=-0.64; p<0.0001). The same was true when the heart rate difference between the 2 treatment modalities at the end of the study was compared with the relative risk reduction for cardiovascular events.

A meta-analysis of 12 randomized controlled trials evaluated 112,177 hypertensive patients for primary prevention of heart failure. Beta-blockers reduced blood pressure compared to placebo, resulting in a 23% (trend) reduction in HF risk (p=0.055).[348] When compared with other agents, the antihypertensive efficacy of beta-blockers was comparable, which resulted in similar but no incremental benefit for HF risk reduction in the overall cohort (risk ratio, 1; 95% CI, 0.92 to 1.08), in the elderly (≥ 60 years) or in the young (< 60 years). Analyses of secondary outcomes showed that beta-blockers confirmed similar but no incremental benefit for the outcomes of all-cause mortality, cardiovascular mortality, and myocardial infarction. Beta-blockers increased stroke risk by 19% in the

elderly (p<0.0001) yet decreased the risk of stroke in the young by 22% compared to other antihypertensives.

A meta-analysis of randomized controlled trials compared beta-blockers, calcium channel blockers (CCBs), and nitrates for angina.[349] Rates of cardiac death and MI were not significantly different for beta-blockers versus CCBs (OR, 0.97; 95% CI, 0.67 to 1.38; p=0.79). Beta-blockers were discontinued due to adverse events less often than CCBs (OR, 0.72; 95% CI, 0.6 to 0.86; p<0.001). Too few trials compared nitrates with calcium antagonists or beta-blockers to draw firm conclusions about relative efficacy.

Two meta-analyses reviewed the use of beta-blockers post MI and found a significant mortality reduction.[350,351] A meta-analysis of beta-blocker use post MI found that the relative benefit of beta-blockers on mortality after a MI is similar in the presence or absence of heart failure.[352]

A meta-analysis of randomized controlled trials of beta-blockers after acute MI found 10% of 54,234 patients randomized to beta-blockers or control died.[353] The review identified a 23% reduction in the odds of death in long term trials (95% CI, 15 to 31), but only a 4% reduction in the odds of death in short term trials (95% CI, -8 to 15). Meta-regression in long term trials did not find a significant difference in effectiveness in drugs with cardioselectivity but did identify an almost significant trend towards decreased benefit in drugs with intrinsic sympathomimetic activity (ISA). The most evidence was available for propranolol, timolol, and metoprolol.

A meta-analysis of 12 randomized controlled studies investigated the efficacy and tolerability of nebivolol compared with other antihypertensive drugs and placebo in patients with hypertension.[354] Antihypertensive response rates (the percentage of patients achieving target BP levels or a defined DBP reduction) were higher with nebivolol than with ACE inhibitors (OR, 1.92; p=0.001) and all antihypertensive drugs combined (OR, 1.41; p=0.001) and similar to beta-blockers, calcium channel blockers (CCBs), and the angiotensin receptor blocker (ARB), losartan. More patients on nebivolol achieved target BP levels compared with patients treated with losartan (OR, 1.98; p=0.004), CCBs (OR, 1.44; p=0.024), and all antihypertensive drugs combined (OR, 1.35; p=0.012). The percentage of patients experiencing adverse events did not differ between nebivolol and placebo; adverse event rates were significantly lower with nebivolol than losartan (OR, 0.52; p=0.016), other beta-blockers (OR, 0.56; p=0.007), nifedipine (OR, 0.49; p<0.001), and all antihypertensive drugs combined (OR, 0.59; p<0.001).

A meta-analysis to evaluate the efficacy of sotalol in the prevention of postoperative supraventricular tachyarrhythmias was performed.[355] A systematic review produced 15 eligible publications that provided 20 comparisons of sotalol with a control group. The incidence and relative risk (RR) with 95% confidence interval (CI) of developing postoperative supraventricular tachyarrhythmias while taking sotalol were, sotalol (n=489) versus placebo (n=499): 22.5% versus 41.5%, RR=0.55 (CI, 0.454 to0.667, p<0.001); sotalol (n=304) versus no treatment (n=311): 12% versus 39%, RR=0.329 (CI, 0.236 to 0.459, p<0.001); sotalol (n=488) versus beta-blocker (n=555): 14% versus 23%, RR=0.644 (CI, 0.495 to 0.838, p<0.001); sotalol (n=139) versus amiodarone (n=146): no significant differences in supraventricular tachyarrhythmia prevention; and sotalol (n=51) versus magnesium (n=54): no significant differences in supraventricular tachyarrhythmia prevention. Whether sotalol is administered orally or intravenously did not significantly affect efficacy. Initiating sotalol after surgery (as opposed to preoperatively) showed a trend toward less adverse events (before: RR=1.7 [CI, 0.903 to 3.200] and after: RR=0.767 [CI, 0.391 to 1.505]).

SUMMARY

All beta-blockers have similar efficacy for the treatment of hypertension (HTN). The role of beta-blockers in primary prevention for hypertension has been questioned. The 2014 Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) HTN guidelines and the 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/Centers for Disease Control and Prevention (CDC) HTN scientific advisory recommend diuretics as first-line for pharmacotherapy. If elevated blood pressure persists, combination therapy is warranted. Beta-blockers are not appropriate as first-line agents and are recommended only if a compelling indication such as stable heart failure, myocardial infarction (MI), angina, and tachyarrhythmias exists.

All beta-blockers are equally effective in treating stable angina. The 2007 ACC/AHA chronic stable angina guidelines recommend indefinite beta-blocker therapy for blood pressure control in patients with coronary artery disease (CAD), and in all patients who have had an MI, acute coronary syndrome (ACS), or left ventricular dysfunction (LVD), with or without heart failure symptoms. Beta-blockers without intrinsic sympathomimetic activity (ISA) are preferred, since those with ISA may not decrease heart rate and blood pressure at rest.

Beta-blockers reduce morbidity and mortality and are considered the standard of care in patients with a prior MI. The 2014 ACC/AHA guidelines for non-ST coronary syndromes and the American College of Cardiology Foundation (ACCF)/AHA 2013 ST-segment elevation myocardial infarction guidelines recommend indefinite beta-blocker therapy in all hemodynamically stable patients with unstable angina and MI. The 2007 AHA HTN guidelines in ischemic heart disease prefer cardioselective beta-blockers without ISA in these patients.

Bisoprolol, metoprolol succinate ER (Toprol XL, Kapspargo Sprinkles), and carvedilol (Coreg, Coreg CR) all have clinical data to support their use in the management of heart failure (HF); however, only metoprolol succinate ER and carvedilol are FDA-approved for heart failure. The 2013 ACC/AHA HF guidelines recommend using one of the following beta-blockers for HF: bisoprolol, carvedilol, or metoprolol succinate ER.

Ventricular arrhythmias contribute to the increased risk for sudden cardiac death in patients with HF and MI. The 2006 ACC/AHA/European Society of Cardiology (ESC) guidelines for ventricular arrhythmias and prevention of sudden cardiac death recommend beta-blockers as standard of care.

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